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Control of Reflexive Saccades following Hemispherectomy

Patricia A. Reuter-Lorenz[1], Troy M. Herter[2], and Daniel Guitton[2]

Abstract

■ Individuals who have undergone hemispherectomy for treatment of intractable epilepsy offer a rare and valuable opportunity to examine the ability of a single cortical hemisphere to control oculomotor performance. We used peripheral auditory events to trigger saccades, thereby circumventing dense postsurgical hemianopia. In an antisaccade task, patients generated numerous unintended short-latency saccades toward contralesional auditory events, indicating pronounced limitations in the ability of a single hemicortex to exert normal inhibitory control over ipsilateral (i.e., contralesional) reflexive saccade generation. Despite reflexive errors, patients retained an ability to generate correct antisaccades in both directions. The prosaccade task revealed numerous contralesional express saccades, a robust contralesional gap effect, but the *absence* of both effects for ipsilesional saccades. These results indicate limits to the saccadic control capabilities following hemispherectomy: A single hemicortex can mediate antisaccades in both directions, but plasticity does not extend fully to the bilateral inhibition of reflexive saccades. We posit that these effects are due to altered control dynamics that reduce the responsivity of the superior colliculus on the intact side and facilitate the release of an auditory-evoked ocular grasp reflex into the blind hemifield that the intact hemicortex has difficulty suppressing. ■

INTRODUCTION

Humans explore the sensory world using saccadic eye movements ranging from reflexive glances toward novel, sudden events to voluntary exploration of actual or remembered locations in the world (reviewed in Leigh & Zee, 2006). Control of this repertoire of saccadic eye movements originates from a bilateral network of cortical and subcortical brain regions that include, most notably, the frontal and parietal eye fields, and the superior colliculus (SC). In the normal brain, it is generally accepted that each cortical hemisphere drives saccades directed contralateral to itself. Individuals who have undergone callosotomy or hemispherectomy for treatment of epilepsy retain a capacity for bidirectional control of voluntary saccades by a single intact hemisphere (Herter & Guitton, 2004; Hughes, Reuter-Lorenz, Fendrich, & Gazzaniga, 1992; Tusa, Zee, & Herdman, 1986; Sharpe, Lo, & Rabinovitch, 1979; Troost, Weber, & Daroff, 1972). However, the potential for a single hemicortex to acquire functional control of saccade suppression and the ability to modulate reflexive glances normally and bilaterally have not been explored. This investigation therefore aimed to characterize a single hemisphere's capacity for bilateral control of saccadic reflexes and to identify potential limits on the plasticity of lateralized saccadic control.

Hemispherectomy involves the neurosurgical removal of an entire cortical hemisphere in some patients, or partial removal and complete disconnection of the remaining cortex in others (Ptito & Leh, 2007). Human autopsy and animal models indicate that the ipsilesional thalamus and other subcortical structures undergo extensive retrograde degeneration (Theoret, Boire, Herbin, & Ptito, 2001; Ptito, Herbin, Boire, & Ptito, 1996; Ueke, 1966). The SC, however, is conserved bilaterally after hemispherectomy (Theoret et al., 2001; Ptito et al., 1996; Ueke, 1966), suggesting that the capacity to generate reflexive contralesional saccades might also be preserved. The capacity for blindsight has been studied extensively following hemispherectomy (see Ptito & Leh, 2007 for a review), however, reflexive saccadic behavior has not been systematically studied in these patients primarily due to the dense postsurgical hemianopia that severely limits visually evoked contralesional saccades. To circumvent limitations caused by permanent hemianopia, we examined auditory-evoked saccades to left- and right-sided peripheral tones that these patients can easily localize (Zatorre, Ptito, & Villemure, 1995).

The antisaccade task has proven to be an excellent tool for assessing the limits of saccadic control (Hallett, 1978; reviewed in Ramat, Leigh, Zee, & Optican, 2007; Leigh & Kennard, 2004; Munoz & Everling, 2004). Two key capacities that can be evaluated with this task are the ability to inhibit a prepotent, reflexive response to a stimulus onset (prosaccade) and the capability to perform voluntary saccades in the direction opposite to the sensory stimulus (antisaccade). Notably, studies of patients with focal lesions indicate that damage to dorsolateral prefrontal cortex (e.g., Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991; Guitton, Buchtel, & Douglas, 1985) and/or frontal eye fields (Machado & Rafal, 2004a; see also Henik, Rafal, & Rhodes, 1994) can impair the suppression of reflexive saccades especially in the contralesional direction (see Muri & Nyffeler, 2008, for a review), leading to release of the "visual grasp reflex" (Hess,

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Bürgi, & Bucher, 1946). Regions of posterior parietal cortex have been implicated in the vector inversion required to generate a saccade in the direction opposite to the visual stimulus (e.g., Nyffeler, Rivaud-Pechoux, Pierrot-Deseilligny, Diallo, & Gaymard, 2007). Chronic lesions affecting the intraparietal sulcus have also been shown to reduce the grasp reflex toward contralesional stimuli and increase the latencies of antisaccades in the opposite direction (Rafal, 2006; Machado & Rafal, 2004a). It is unknown how the chronic absence of all oculomotor cortex unilaterally will affect the ability to perform antisaccades.

Reflexive saccade behavior has also been fruitfully examined by varying the state of the fixation stimulus relative to the onset of the signal to saccade (reviewed in Leigh & Zee, 2006). Compared to the overlap condition in which the fixation point remains visible during the signal to saccade, extinguishing the fixation point several hundred milliseconds before the onset of the saccade signal (the gap condition) enables shorter-latency saccades including express saccades with latencies ranging from 80 to 130 msec (Saslow, 1967). In humans, damage to posterior parietal cortex, especially in the right hemisphere, has been associated with increased visual saccade latency in the gap condition (Braun, Weber, Mergner, & Schulte-Mönting, 1992; Pierrot-Deseilligny et al., 1991; however, see Rafal, 2006).

Here we use gap and overlap versions of the antisaccade task to examine whether hemispherectomized patients have the ability to volitionally inhibit stimulus-bound saccades. The prosaccade task is also examined under gap and overlap conditions to further assess reflexive responding and its modulation by fixation. We show that hemispherectomy leads to impaired control of reflexive saccadic behavior including the release of unintended contralesional saccades in the antisaccade task, and the attenuation of the gap effect for ipsilesional prosaccades. We posit that these effects are due to a limited ability of the intact hemisphere to exert top–down control of the ipsilesional SC, and altered control dynamics affecting the SC in the intact hemisphere.

METHODS

Subjects

Three hemispherectomized patients (D. R., I. G., J. B.; see Figure 1 for structural MR images) and four age-matched neurologically intact control subjects participated in this investigation. Detailed descriptions of these patients have been previously published (Zatorre et al., 1995 [D. R.: Case 1; I. G.: Case 5; J. B.: Case 3]; Leh, Johansen-Berg, & Ptito, 2006) and dense contralesional hemianopia has been established in all three patients (Herter & Guitton, 2004, 2007; Leh et al., 2006; Tomaiuolo, Ptito, Marzi, Paus, & Ptito, 1997). In brief, D. R. and I. G. are right-handed women, ages 25 and 47 years, respectively, at time of testing, both of whom underwent right hemispherectomy (Villemure & Mascott, 1995; Villemure & Rasmussen, 1990). D. R. suffered from Rasmussen's chronic encephalitis with seizure onset at age 5. At 17 years, she underwent modified right hemispherectomy that included removal of the temporal lobe, a frontal–parietal corticectomy. All remaining cortical tissue on the decorticate side was surgically disconnected from the rest of the brain, leaving her with a complete functional hemispherectomy. I. G. suffered a prenatal middle cerebral artery occlusion with seizure onset at age 7 and underwent complete anatomical hemispherectomy at age 13, removing her entire cortical hemisphere and homolateral basal ganglia. J. B. is a left-handed man, aged 34 at the time of testing, who underwent left hemispherectomy at age 20 for treatment of seizure disorder with onset at age 5 due to a porencephalic cyst. This included removal of the temporal, parietal, and occipital cortices, and disconnection of any remaining cortex from the rest of the

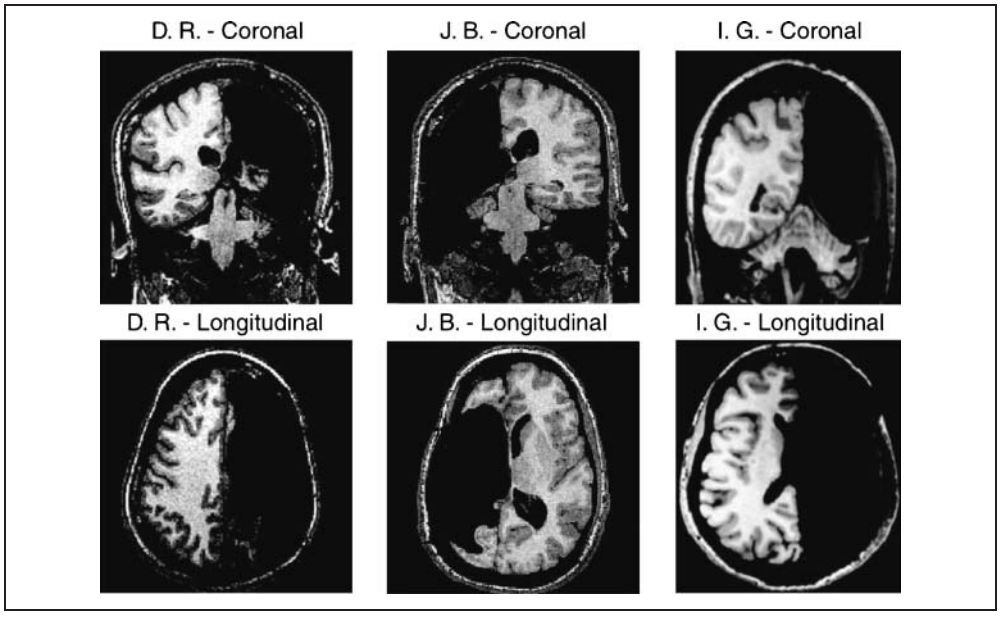

Figure 1. MRIs of the three hemispherectomy patients. The left side of the image corresponds to the left side of the brain in all images. The complete right hemispherectomy of Patient D. R. is shown in the coronal and longitudinal planes, and likewise for Patient I. G. The partial left hemispherectomy of Patient J. B. is shown in the coronal and longitudinal planes.

brain. Preoperative testing determined that he was left-handed with language lateralized to the right cortical hemisphere, permitting left hemispherectomy. The frontal and occipital poles were left in place but were surgically disconnected from the rest of the brain, including the intact hemisphere and brainstem structures. All patients' full-scale IQs fell in the low normal range.

Four right-handed control subjects (2 men and 2 women, ranging from 26 to 33 years of age, similar to the patients) with no history of neurological or psychiatric disorders also participated in this study. All participants gave informed consent and all procedures were approved by the Institutional Review Boards of the Montreal Neurological Institute and the University of Michigan.

Apparatus

Subjects were seated in a completely dark room with their heads stabilized by a chin rest and bite bar. They faced a black cylindrical screen located 55 cm from their eyes along the horizontal meridian. Bitemporal EOG was used to measure horizontal eye position. To minimize drifts and noise, the skin was thoroughly cleaned at each point of electrode contact. Fluctuations in the DC offset were further reduced by a short adaptation period before calibration and recording. During recording, small drifts were corrected by automatically resetting the EOG output to zero as the subjects fixated at the start of each trial. Calibration checks occurred as needed and at least every 15 min by having the subjects fixate a target that jumped predictably from $0° \rightarrow +20° \rightarrow 0° \rightarrow -20° \rightarrow 0°$. This target displacement sequence was repeated while the gain adjustments were made to assure a fixed output voltage for the 20° target offset. When properly calibrated and guarded against drifts, the EOG signal was accurate within ±1° over a range of ±30° for all subjects. This was well within our needs because, as explained below, we were interested in saccade latency and direction, not in endpoint accuracy.

Auditory tones (2800 Hz, 90 dB; the signals to which subjects responded) were generated by two small speakers fixed to the front of the cylindrical screen, 45° to the left and right of the fixation light (LED, 0.5° diameter, 670 nm, 12.0 cd/m^2). Because our aim was to study saccadic response times, we placed the speakers at relatively large eccentricities to promote rapid responses (e.g., Yao & Peck, 1997), albeit with decreased precision of localization (e.g., Zatorre et al., 1995). A small response box equipped with two horizontally aligned buttons was placed on the armrest of the subject's chair on the side of the dominant (nonparetic) hand. The subjects were required to saccade or to press the left or right button, depending on the task (see below).

Tasks and Procedure

Four different tasks were run in a block design: antisaccades, antimanual (button-press), prosaccades, promanual. The stimulus conditions were the same in all four tasks; only the instructions varied. In the prosaccade task, participants were instructed to move their eyes "toward the tone as fast as possible"; the promanual task required participants to use their dominant (or nonparetic) hand to press the response button "on the same side as the auditory tone as fast as possible." In the antisaccade task, participants were told to move their eyes "away from the tone as fast as possible." In the antimanual task, participants were instructed to press the response button "on the side opposite to the auditory tone as fast as possible."

Each trial began with a 100-msec alert signal emitted from a centrally located speaker and which informed participants to fixate the central fixation point (FP). A 1200-msec fixation period preceded the command signal which was a 300-msec tone generated from either one of the two speakers positioned 45° to the left or right of FP (see Figure 2). The participant was instructed to maintain their gaze on location of the FP until the peripheral tone sounded, at which time they were to respond in accord with the task instructions. In the "gap" condition, the FP was extinguished 200 msec before the peripheral tone signaled them to respond. In the "overlap" condition, FP remained illuminated for 2000 msec, thus overlapping with the peripheral tone. The peripheral tone sounded on 89% of the trials and the remaining trials were catch trials requiring subjects to withhold their responses. On all trials, a brief auditory warning signal from the central speaker preceded the onset of the peripheral tone by 300 msec. This warning event offset 200 msec prior to target onset, thus coinciding with the offset of the fixation point on gap trials and providing equivalent warning on gap and overlap trials.

In any single session, the order of pro- and antitasks was randomized, except that a saccade task (e.g., prosaccade) was always followed by its manual counterpart (e.g., promanual). A block consisted of 36 trials and contained an equal number of gap and overlap trials that were randomly intermixed. A short practice block (approximately 12 trials), with feedback if necessary, preceded every task to ensure that the participants shifted set and understood the instructions. Sessions included frequent breaks to maximize comfort, and lasted up to 2 hours. Each individual participated in at least two sessions during which a minimum of 200 trials per responses condition were obtained. Patients' sessions were scheduled at least 4 months apart due to their availability.

Data Analysis

Trials were excluded from analysis if the eyes moved beyond a 5° window centered on the fixation point (i.e., ±2.5°) at any point in time between initial fixation of the FP and the onset of the peripheral auditory tone. Blinks were verified by the vertical EOG signal and trials were excluded if blink artifacts prevented accurate detection of saccade onset. Finally, trials were excluded if large drift or noise in the horizontal EOG signal prevented accurate saccade detection.

For Patient D. R., 1–5% of trials were omitted per condition due to artifacts. She showed no differences in

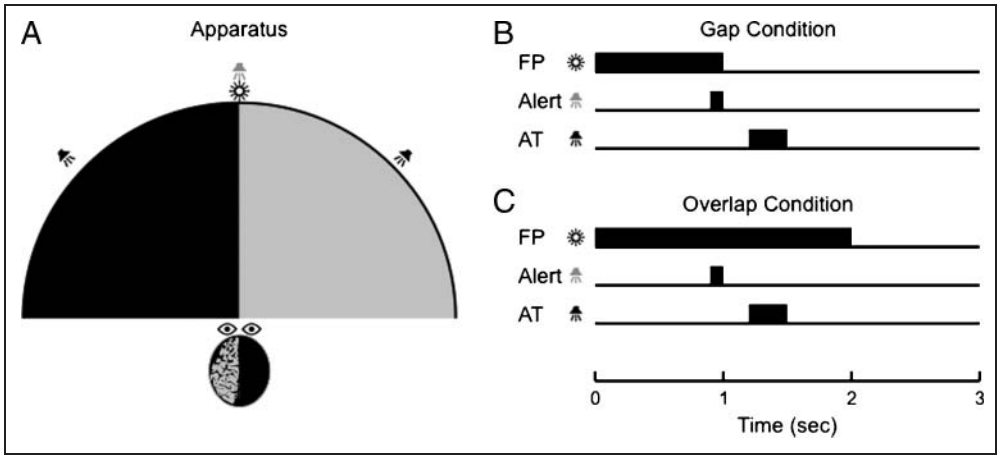

Figure 2. Apparatus and task. (A) Schematic illustration depicting the locations of the auditory tones relative to a cartoon hemispherectomized brain. The intact and blind hemifields are shown contralateral to the intact and ablated hemisphere respectively. (B, C) Timing of the onset and offset of the central fixation point (FP), peripheral auditory tones (AT), and central auditory alert (Alert) in the gap and overlap conditions.

the incidence of excluded ipsilesional, contralesional, or catch trials, nor did exclusions differ for saccade versus manual trials. Patient J. B. had approximately 5% of trials excluded for each antisaccade direction and less than 1% exclusions in all other conditions. Patient I. G. had the largest incidence of excluded trials, most of which occurred in the prosaccade condition and were equally frequent for each stimulus/fixation condition (18%). I. G.'s exclusions for the other conditions varied between 1% and 7% of trials. Across patients there was no consistent pattern in trial exclusions.

Saccade onset was detected as the first of five consecutive points with velocity >20 deg/sec if the amplitude exceeded 1°, and maximum velocity exceeding 50 deg/sec. This time point relative to the onset of the peripheral tone is defined as the saccadic reaction time (SRT). Saccade offset was detected as the first of five consecutive points with velocity <20 deg/sec. Maximum acceptable saccade duration was 500 msec for prosaccades and 800 msec for antisaccades, which tended to be considerably slower especially for the patient group. Saccades that met the above criteria were retained.

This report focuses on SRTs and saccade direction errors. Saccade endpoint accuracy is not considered due to the large stimulus eccentricities. Hemispherectomized patients are also known generally to use different movement strategies to acquire targets in the seeing and blind hemifields (Herter & Guitton, 2007; Traccis, Pulgia, Ruiu, Marras, & Rosati, 1991). Saccade metrics are not considered because the EOG signal is inherently too noisy to permit accurate velocity profiles.

When possible, patient and control performance were compared directly using *t* tests or between-group ANOVA. However, a fully crossed between-group approach was inappropriate for directional analyses because the relevant directional categories differed for the two groups (i.e., contralesional and ipsilesional, categories that were not applicable to the control group). Thus, directional effects were analyzed as a within-group factor, or via between-group *t* tests. Single-patient analyses tested differences between proportions or, in some conditions (correct antisaccade SRTs), single-subject analyses are reported with individual trial responses treated as the random variable.

Express Saccades

Express saccades have latencies in the range of 80–130 msec and are enabled by the gap condition (e.g., Muri et al., 1999; Fischer & Breitmeyer, 1987; Fischer & Ramsperger, 1984; Fischer & Boch, 1983). Few studies have investigated express saccades to auditory targets (Corneil, Van Wanrooij, Munoz, & Van Opstal, 2002; Taylor, Klein, & Munoz, 1999; Shafiq, Stuart, Sandbach, Maruff, & Currie, 1998; Fendrich, Hughes, & Reuter-Lorenz, 1991), thus here we use the same latency range to define auditorily triggered express saccades. Saccades with latencies less than 80 msec were considered anticipatory (Kalesnykas & Hallett, 1987) and were analyzed separately (see Results).

RESULTS

Antisaccade: Error Frequency and Error Latencies

In the antisaccade task, an error was defined as a saccade toward the auditory tone rather than away from it. As can be seen from Figure 3, patients showed a preponderance of saccades to contralesional tones. This pronounced asymmetry between contralesional and ipsilesional errors was present in each patient individually (difference between proportions: all ps $< .01$), and was especially pronounced in the gap condition, as can be seen in Figure 3. This was confirmed in an ANOVA performed on the patients as a group with Fixation Condition (gap/overlap) and Tone Location (ipsi/contra) as repeated within-subject factors. The reliable main effect of Fixation Condition [$F(1, 2) = 22.27$, $p = .042$] and the marginal effect of Tone Location [$F(1, 2) = 10.51$, $p = .08$] were moderated by a reliable interaction of Fixation Condition and Tone Location [$F(1, 2) = 23.80$, $p = .04$]: Contralesional reflexive errors were more frequent in the gap than overlap condition, whereas

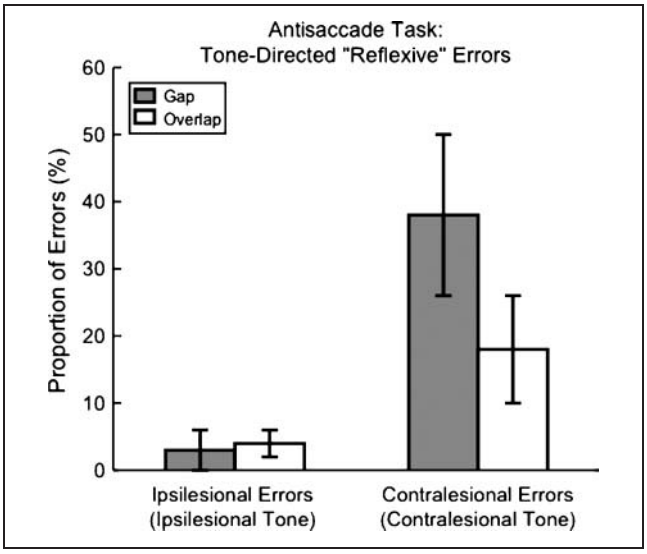

Figure 3. Tone-directed "reflexive" errors in the antisaccade task. Group means of contralesional and ipsilesional "reflexive" errors by the patients in the gap (gray bars) and overlap (white bars) conditions. By comparison, control subjects (not shown) generated "reflexive" errors on less than 6% of trials. Error bars indicate 95% confidence interval.

ipsilesional errors were unaffected by fixation point condition (see Figure 3).

Patients' pronounced error asymmetry was markedly unlike controls. The control group made only 41 directional errors in total, amounting to 5.5% error rates in each direction and a minimal difference between the gap and overlap conditions (6% vs. 5%). Paired t tests indicate that the overall rate of contralesional errors for patients is significantly greater than the overall error rate for controls [28% vs. 5.5%, respectively; $t(5) = 2.11$, $p = .04$], whereas the rate of ipsilesional errors is approximately equivalent to the average error rate for controls (patients: 3.6% and controls: 5.5%,). Indeed, with ipsilesional tones, patients' error rates were in the range of the control group, which was between 2% and 9%. These results indicate that patients' antisaccade performance was associated with a specific and significant increase in erroneous contralesional saccades, especially in the gap condition. Critically, 97% of the patients' errors in the antisaccade task were followed immediately by a saccade in the opposite correct direction, away from the eccentric auditory tone. This highly reliable corrective behavior indicates that the patients knew the correct response but were unable to suppress stimulus-bound saccades.

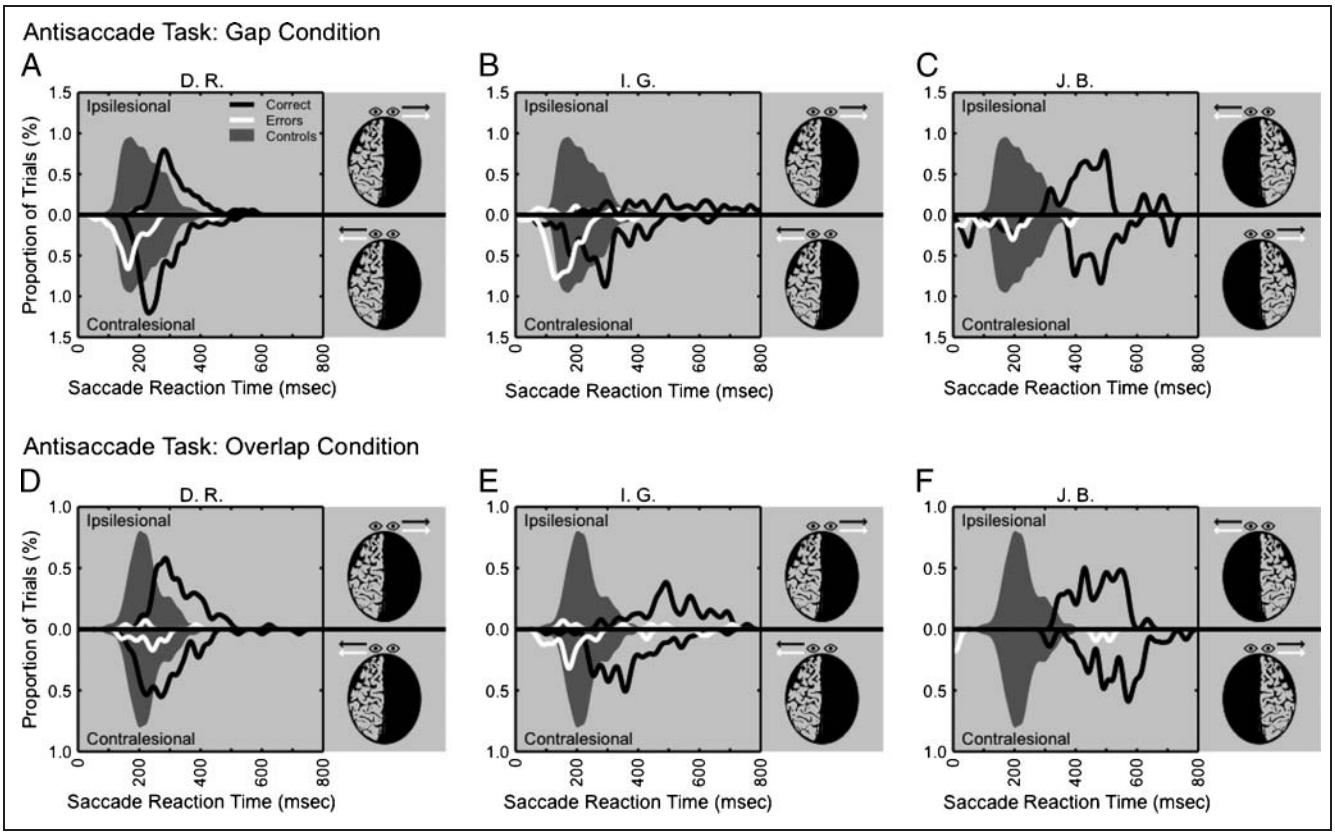

Figure 4. SRT distributions of each patient in the antisaccade task. SRT histograms of correct antisaccades (black) and tone-directed "reflexive" errors (white) are illustrated for the gap (A–C) and overlap (D–F) conditions. Ipsilesional antisaccades and "reflexive" errors are displayed beside their corresponding task schemata in the upper half of each panel. Contralesional antisaccades and "reflexive" errors are displayed beside their corresponding task schemata in the lower half of each panel. Patient histograms are superimposed on the group SRT histogram of the control subjects (dark gray fill). Ipsilesional and contralesional refer to the direction of correct antisaccades and "reflexive" errors.

The latency distributions of these errors are consistent with their reflexive nature (see Figure 4 which also shows patients' histograms superimposed on the composite histogram derived from the control group). For the patients, nearly 24% of the contralesionally directed errors in the antisaccade gap condition had express saccade latencies. Ipsilesionally directed errors were so rare as to preclude any meaningful latency analyses. Similarly, the low error rates for the control subjects precluded statistical analyses of latencies, however, pooling errors across individuals resulted in an overall average error SRT of 164 msec (anticipatory errors excluded). For both groups, only 2% of responses were anticipatory and for patients these were equally ipsilesional and contralesional. Responses occurred on less that 1% of catch trials.

Correct Antisaccades: Average SRT and Gap Effects

Despite numerous reflexive errors to contralesional tones, all patients generated at least 30 correct antisaccades per direction, which permitted analyses of latency and gap effects. The antisaccade SRT data are somewhat more variable than other measures, thus the results for individual patients will be presented first. Figure 4 shows histograms for each patient individually and Table 1 provides mean RTs and gap effects. Two patients (Patient D. R., Figure 4A, D; Patient I. G., Figure 4B, E) generated longer latency antisaccades in the ipsilesional direction than in the contralesional direction, and this directional asymmetry in SRTs was significant in both the gap and the overlap conditions (for all ps $< .01$). Patient J. B.'s antisaccade latencies were slower overall (Figure 4C, F) and did not differ due to direction ($p = .18$). Two patients, I. G. and J. B., also showed a marked asymmetry in the magnitude of the gap effect. Both produced highly significant gap effects for contralesional antisaccades (both patients: $p < .01$), but lacked any such effect for ipsilesional antisaccades. D. R. did not show a reliable gap effect in either direction.

A between-group ANOVA, collapsing across directions, indicated patients were slower to initiate antisaccade than controls [$F(1, 5) = 12.09, p < .018$]. A main effect for fixation condition indicated that both groups had faster SRTs in the gap than overlap condition [$F(1, 5) = 12.66, p < .016$]. The controls averaged 216 msec for the gap condition and 229 msec for the overlap condition, whereas the patients averaged 383 and 413 msec, respectively. Although the magnitude of the gap effects was quantitatively larger for patients than controls (33 vs. 13 msec, respectively), this difference did not reach significance [$F(1, 15) = 5.11, p = .07$]. Note that the 13-msec antisaccade gap effect for controls is considerably smaller than the effect for prosaccades (see below), but commensurate with the magnitudes found for these responses in previous studies (Craig, 1999; Fischer & Weber, 1997; Reuter-Lorenz, Oonk, Barnes, & Hughes, 1995; Reuter-Lorenz, Hughes, & Fendrich, 1991).

Table 1. Reaction Time (Mean ± *SEM*) for Correct Trials

			Patients Combined		*D. R.*		*I. G.*		*J. B.*	
Task	*Condition*	*Controls*	*Contralesional*	*Ipsilesional*	*Contralesional*	*Ipsilesional*	*Contralesional*	*Ipsilesional*	*Contralesional*	*Ipsilesional*
Antisaccade	Gap	216 ± 21	337 ± 54	430 ± 56	274 ± 8	321 ± 10	291 ± 12	508 ± 27	445 ± 24	460 ± 17
	Overlap	229 ± 17	393 ± 71	437 ± 56	288 ± 10	328 ± 9	361 ± 12	514 ± 15	529 ± 15	470 ± 12
	Gap effect	13	56	7	14	7	70	6	84	10
Antimanual	Gap	334 ± 25	602 ± 108	594 ± 122	411 ± 9	381 ± 9	784 ± 13	804 ± 16	612 ± 19	598 ± 20
	Overlap	339 ± 26	611 ± 81	595 ± 118	467 ± 16	381 ± 8	749 ± 15	787 ± 15	618 ± 17	617 ± 19
	Gap effect	5	9	1	56	0	−35	−17	6	19
Prosaccade	Gap	156 ± 8	181 ± 30	267 ± 47	142 ± 4	199 ± 9	160 ± 11	246 ± 11	240 ± 15	357 ± 9
	Overlap	179 ± 10	224 ± 38	273 ± 51	179 ± 7	205 ± 9	194 ± 11	241 ± 9	299 ± 12	372 ± 9
	Gap effect	23	43	6	37	6	34	−5	59	15
Promanual	Gap	267 ± 15	450 ± 76	508 ± 103	313 ± 9	323 ± 8	577 ± 15	678 ± 16	460 ± 12	523 ± 9
	Overlap	268 ± 15	442 ± 83	493 ± 108	293 ± 8	294 ± 8	578 ± 14	669 ± 14	454 ± 13	516 ± 17
	Gap effect	1	−8	−15	−20	−29	1	−9	−6	−7

Contralesional and ipsilesional refer to the direction of the response.

Antimanual: Errors and Response Times

Directional errors in the antimanual task were rare. Patients made less than 2% errors, with no asymmetries. Controls made more errors than patients (range: 2–11%), most likely because they were responding faster and were more inclined to trade accuracy for speed. The overall response latency for patients was 597 msec (SE = 107), which was reliably slower than the average for controls, which was 336 msec (SE = 26.3) (Table 1). Neither group showed a reliable effect of fixation condition or direction. Stimulus-directed manual responses are less prepotent than saccades, which limits the conclusions we can draw from this control condition. Nevertheless, the patients' accurate and symmetrical manual performance demonstrates their ability to accurately localize tones to the left and right of auditory space. It also indicates they were fully able to remember and follow rules, and to maintain an incompatible stimulus–response mapping, difficulties that have been associated with frontal dysfunction, and which could have contributed to poor antisaccade performance.

Prosaccades: Express Saccade Frequency

Figure 5A–F present the frequency distributions of SRTs in the prosaccade gap and overlap conditions for ipsilesional (upper panels) and contralesional (lower panels) tones for each patient. Saccades in the express range were more frequent in the gap than overlap conditions [collapsing across directions: patients, 21.2% vs. 5.5%, $t(2) = 4.85, p = .02$; controls, 25% vs. 12%, $t(3) = 2.95, p = .03$]. This can be seen by comparing Figure 5D–F, which show the SRT distributions for the overlap condition, with Figure 5A–C, which show the distributions for the gap condition.

For all patients individually, proportions of express responses were significantly greater to contralesional than ipsilesional tones (all ps $< .05$): For D. R., the percentage of express saccades was 40% contralesionally versus 9% ipsilesionally; for I. G., 37% versus 11%; for J. B., 18% versus 0%. Across the group, these values were 32% versus 7% [$t(2) = 4.61, p = .02$]. Controls generated equivalent percentages of left and right express saccades; 26% and 24%, respectively; a nonsignificant difference. Thus, patients showed a pronounced directional asymmetry for prosaccades in the gap condition with a disproportionate incidence of contralesional express saccades and a low incidence of ipsilesional express saccades (i.e., in the preferred direction of the intact hemisphere).

Prosaccades: Average Response Times and Gap Effects

All patients individually also showed a pronounced asymmetry in the gap effect (Table 1). A group analysis confirmed that the gap effect was significantly greater for contralesional than ipsilesional prosaccades [43 and 6 msec, respectively; $t(2) = 10.03, p < .004$]. Controls showed a significant gap effect of 23 msec [$t(3) = 5.0, p < .02$] that did not differ in magnitude for leftward and rightward prosaccades [$t(3) = 1.7, p > .10$].

As a group and collapsing across fixation condition and directions, the patients generated longer latency prosaccades than the controls (235 and 167 msec, respectively), although this difference was not statistically reliable [$t(5) = 1.3, p > .1$]. However, as expected, given the asymmetry in express saccade rates, patients showed an overall asymmetry in saccadic latency, with faster contralesional than ipsilesional saccades [201 vs. 270 msec; $t(3) = 4.39, p < .05$]. Controls showed no difference in latencies between left versus right saccades (165 vs. 169 msec, *ns*).

Prosaccades: Anticipatory and Catch Trial Responses

We examined the possibility that the patients' contralesional express saccades were anticipatory or otherwise erratic responses rather than being stimulus triggered. Two features of the data indicate that they are likely stimulus triggered. First, anticipatory responses (SRTs less than 80 msec) occurred at approximately the same frequency for trials with ipsilesional and contralesional tones (9.5% and 11.3%, respectively; $p > .10$), although saccades in the express range were much more frequent in the latter condition. (Patients' anticipations were more frequent than controls' who averaged approximately 2%.) Second, 91% of all express saccades were in the correct direction, whereas only 57% (i.e., not different from chance) of saccades classified as anticipatory were correct. This argues that the express saccades were stimulus triggered, whereas the anticipatory saccades were not (Findlay & Walker, 1999). It is also noteworthy that compared to controls, who averaged 3.5% catch trial responses, the patients frequently made saccades on catch trials, but most of these were long latency responses, suggesting they were breaks in fixation. I. G. generated an equal proportion of contralesional and ipsilesional catch responses (31% and 29%, respectively), with average latencies of 384 and 455 msec, respectively, which were also slower than her target-directed responses. J. B. generated contralesional responses on 42% of the catch trials, and ipsilesional responses on 17% of these trials, with most responses falling beyond the 500 msec cutoff and averaging 964 and 1400 msec, respectively. D. R. responded on 97% of catch trials always with saccades directed contralesionally. Again the latencies were considerably longer than the target-directed responses, averaging 425 msec on gap trials and 919 msec on overlap trials. Taken together, the results from anticipatory and catch trial responses argue that the highly frequent contralesional express saccades were indeed stimulus-triggered responses.

Promanual: Errors and Response Times

Although controls responded faster than the patients [collapsing across direction and condition: 267 and 478 msec, respectively; $F(1, 5) = 6.82, p < .05$], there were no group

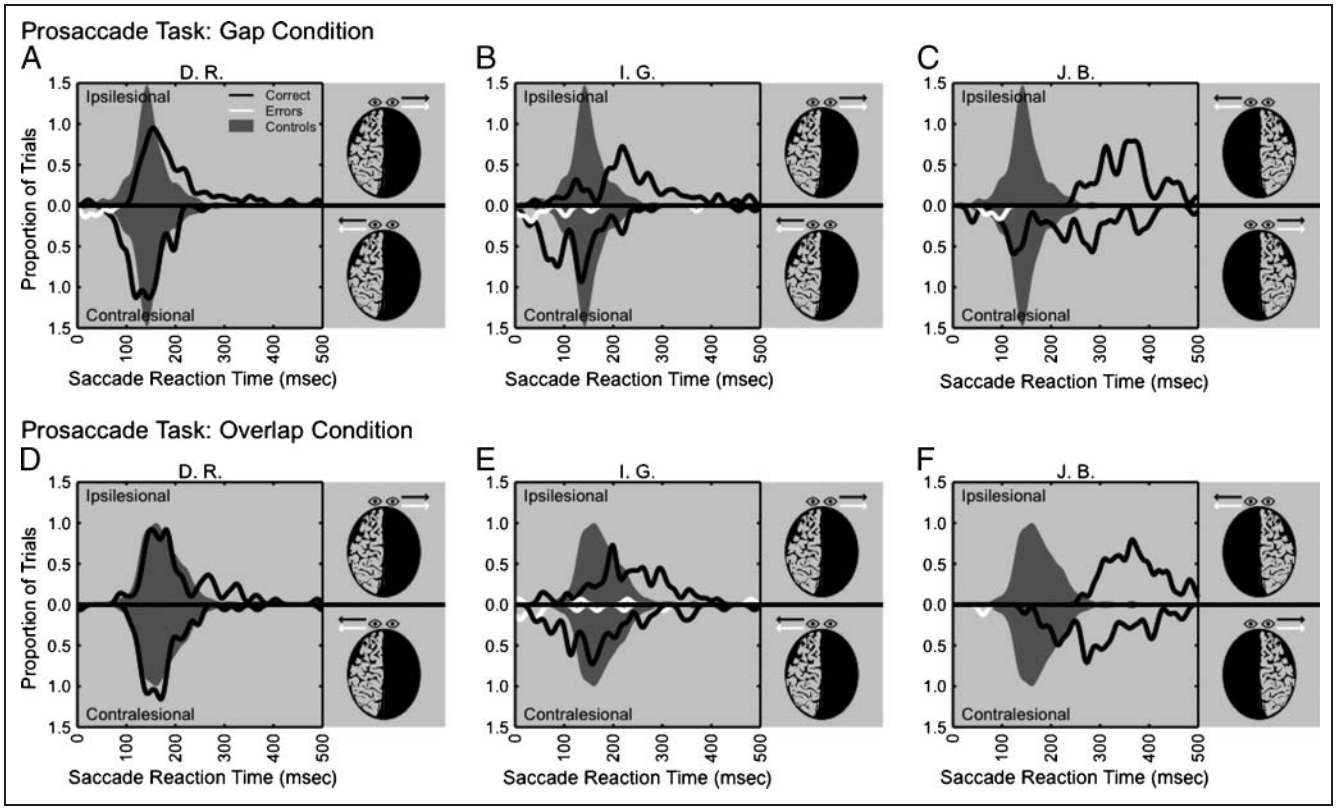

Figure 5. SRT distributions of each patient in the prosaccade task. SRT histograms of correct prosaccades (black) and erroneous antisaccades (white) are shown for the gap (A–C) and overlap (D–F) conditions. Histograms are displayed beside their corresponding task schemata in the upper and lower half of each panel. Patient histograms are superimposed on the group SRT histogram of the control subjects (dark gray fill). Contralesional and ipsilesional refer to the direction of correct prosaccades and erroneous antisaccades.

differences in the patterns of promanual performance. Neither group showed an effect of fixation or tone direction. Errors were rare (1–4 per subject) and equivalent for both groups. The patients' slow manual RTs are consistent with their performance in other manual response tasks (e.g., Tomaiuolo et al., 1997). In addition to confirming the ability to accurately localize the left and right tones, the largely symmetrical manual RTs rule out a general attentional orienting deficit that could result from parietal ablation (e.g., Rafal, 2006).

DISCUSSION

The primary objective of this study was to examine the effect of hemispherectomy on the control of reflexive saccadic behavior. By using easily localized auditory cues, we could effectively examine stimulus-bound saccadic responses otherwise masked by hemianopia. An important and especially novel result is that hemispherectomized patients showed a pronounced tendency to generate unintended contralesional saccades (Figure 3) driven by an auditory event in the blind hemifield. This reflexive saccadic behavior, not previously documented in these patients, was evident in the highly asymmetrical incidence of disallowed prosaccade errors especially in the gap condition of the antisaccade task, many of which were in the express saccade range. Moreover, these stimulus-bound responses were consistently followed by a correct antisaccade in the ipsilesional direction, as would be expected if the errors were unintended. Likewise, the prosaccade task revealed numerous contralesional express saccades, a robust contralesional gap effect, but the absence of both effects for ipsilesional saccades. The release of reflexive contralesional saccades indicates reduced control and possibly hyperactivity of the ipsilesional SC following hemispherectomy. Furthermore, reduced gap effects and express saccades ipsilesionally suggest that hemispherectomy alters saccadic control by the intact hemisphere, which may result from altered collicular dynamics and concomitant hypoactivity of the contralesional SC.

How do the current findings compare with prior reports of patients with chronic focal lesions of oculomotor cortex? One especially noteworthy difference is that the saccadic "release" behaviors documented here following hemispherectomy were displayed into a blind hemifield, and were thus unmasked by sudden peripheral auditory events, which could be adequately localized by spared subcortical regions, and the intact cortex. Studies of patients with focal lesions have examined visually guided saccades into sighted hemifields, thus little is known about their saccadic responses to auditory events. That said, our observations regarding both latency and antisaccade errors are not

easily deduced by combining the results of frontal and parietal lesions described in the literature. In particular, the present results are compatible with previous observations in frontal lobe patients who generated a high incidence of erroneous contralesional stimulus-bound saccades in a visual antisaccade task (Machado & Rafal, 2004a; Guitton et al., 1985). This suggests that an absence of frontal control may be especially important for the contralesional reflexive errors reported here in hemispherectomized patients (see also Gaymard, Ploner, Rivaud, Vermersch, & Pierrot-Deseilligny, 1998; Henik et al., 1994). However, some frontal patients have a high percentage of errors bilaterally (Guitton et al., 1985), and others are completely unable to generate a correct antisaccade in the dark. Neither of these attributes characterized our patients, who showed a far more specific impairment. Furthermore, Machado and Rafal (2004a) have documented hyporeactivity due to chronic parietal damage, such that patients generate fewer contralesional visual grasp errors compared to controls. Lateralized parietal damage has generally weaker effects on stimulus-bound errors than prefrontal damage, but these effects are, nevertheless, opposing, suggesting the unlikely consequence that their combined effects would cancel one another. Thus, the dominance of contralesional errors observed in the present study cannot be predicted from the theoretical "sum" of deficits following restricted lesions.

Despite numerous contralesional reflexive errors, all patients were able to produce a subset of correct antisaccades. This preserved ability for a single hemisphere to generate bilateral saccades is presumably mediated via innate bilateral projections to brain stem structures including the SC, the nucleus reticularis tegmenti pontis, and the paramedian pontine reticular formation (Stanton, Goldberg, & Bruce, 1988; Huerta, Krubitzer, & Kaas, 1986; Leichnetz, Smith, & Spencer, 1984; Leichnetz, Spencer, Hardy, & Astruc, 1981; see Herter & Guitton, 2004; Hughes et al., 1992 for a review). Furthermore, the remaining cortical hemisphere retained the ability to perform the vector inversion required for the successful initiation of these responses. Although this ability is thought to rely on frontal–parietal and bilateral parietal–parietal interactions (Rafal, 2006; Munoz & Everling, 2004), the successful antisaccade performance of our hemispherectomized sample indicates that a single intact hemisphere can assume the ability to perform the necessary sensorimotor transformations at least for auditory stimuli. The pronounced incidence of unintended contralesional saccades, however, suggests the remaining networks have limited ability to mediate the inhibition of reflexive saccades contralesionally. Additionally, the fact that the residual deficits align more with those due to unilateral lesions of frontal than parietal oculomotor cortex suggests greater neuroplasticity and compensation for parietal than frontal loss.

Furthermore, the present investigation revealed conditions under which the triggering of ipsilesional prosaccades generated by the intact hemisphere have been altered, leading to the absence of a gap effect and express latencies for ipsilesional saccades. It is worth noting that longer latency ipsilesional saccades have also been reported in patients with focal lesions affecting the frontal eye fields (Machado & Rafal, 2004b; Henik et al., 1994). In contrast to the effects of unilateral frontal eye field lesions, we find that hemispherectomy also reduced the modulatory effects of a fixation stimulus on *ipsilesional* saccade generation. Together, these changes in ipsilesional prosaccades suggest altered responsivity of the SC on the intact side.

The absence of cortical input unilaterally following hemispherectomy is likely to have an important influence on the tonic activity level of the SC, leading to altered interactions between the left and right SC (reviewed in Takahashi, Sugiuchi, Izawa, & Shinoda, 2005; Keller, 2004; Munoz & Fecteau, 2002; Sparks, 2002; Sprague, 1966) and asymmetries in orienting control (Sprague, 1966). Furthermore, Everling and Munoz (2000), Everling, Dorris, Klein, and Munoz (1999), Dorris and Munoz (1995, 1998), Everling, Dorris, and Munoz (1998), and Dorris, Pare, and Munoz (1997) have shown that express saccades, the gap effect, and antisaccade performance are all associated with modulation of preparatory motor activity in saccade-related and fixation neurons in the SC.

We speculate that hemispherectomy may produce an asymmetric preparatory state across the two sides of the SC given evidence that preparatory activity in each SC may be suppressed directly by ipsilateral cortex (Johnston & Everling, 2006) and/or indirectly through the ipsilateral or contralateral basal ganglia (Jiang, Stein, & McHaffie, 2003; Hikosaka & Wurtz, 1983; reviewed in Munoz & Everling, 2004; Hikosaka, Takikawa, & Kawagoe, 2000). The high frequency of contralesional errors in the antisaccade task, together with the high frequency of contralesional express saccades during the prosaccade task, is compatible with a higher level of preparatory motor activity in the ipsilesional SC. The paucity of reflexive ipsilesional saccades and the absence of a gap effect ipsilesionally suggest the concomitant reduction in motor preparatory activity in the SC in the intact hemisphere, which could result from decreased modulation of fixation-related processes (e.g., Hood & Atkinson, 1993), increased inhibitory influence via intercollicular commissural projections (Sprague, 1966), or both.

Although it is unknown whether this hypothesized asymmetry in SC activity would prevail under all sensory environments (e.g., with ambient lighting), one might speculate that asymmetric SC activity could advantageously enable hemispherectomized patients to gaze rapidly toward auditory stimuli in their blind hemifield. If such compensatory adjustments were adaptations to chronic hemianopia, they might also be expected to result from blindness due to focal occipital lobe lesions, for example. To our knowledge, no such effects have been reported. We note, however, that auditory accessory stimuli presented in spatial register with visual stimuli appearing in the blind field have been especially effective in the recovery of oculomotor scanning into the blind field of hemianopic patients (Passamonti, Bertini, & Ladavas, 2009; Bolognini, Rasi, Coccia, & Ladavas,

2005). Such results, together with the present evidence favoring preserved collicular oculomotor function, suggest the potential benefits of utilizing the auditory modality to unmask and potentially rehabilitate contralesional orienting capabilities.

In summary, our data reveal several novel oculomotor sequelae of hemispherectomy that shed new light on the dynamics of saccadic control. First, a single hemisphere is not fully able to suppress reflexive glances bilaterally, leading to release of a contralesional "auditory-evoked ocular grasp reflex" into an otherwise blind hemifield. Second, despite these reflexive errors, a single cortical hemisphere is capable of performing antisaccades in either direction in response to an auditory event. Finally, our data indicate alterations in saccadic control by the SC in the intact hemisphere, suggesting some chronic imbalance in intracollicular activity caused by hemispherectomy.

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